

# In Vitro Pharmacology and Phase 1/2 Results of VRDN-001, a Full Antagonist Antibody to IGF-1 Receptor for Thyroid Eye Disease (TED)

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# Disclosures

- These studies were sponsored by Viridian Therapeutics, Inc. All data are proprietary.
- **VRDN-001** is an investigational therapy not approved in any country. All authors met the ICMJE authorship criteria and had full access to relevant data.
- All data from the active TED phase 2 proof-of-concept study are as of data cutoff of December 19, 2022.
- Presenting author: Raymond S. Douglas is a consultant and clinical research investigator for Horizon Therapeutics and Viridian Therapeutics, Inc.
- Coauthors: Roger E. Turbin, Kimberly Cockerham, Navdeep Nijhawan, Rosa Tang, Michael T. Yen, Chantal Boisvert, David Kaufman, Andrea Kossler, Wendy W. Lee, Michael Yoon, and Shoaib Ugradar have consulted for, conducted studies funded by, or received honoraria for services provided to Viridian Therapeutics, Inc. Vahe Bedian and Barrett Katz are employees of Viridian Therapeutics, Inc.
- The authors would like to thank the study investigators, research teams, and study participants who make this research possible.

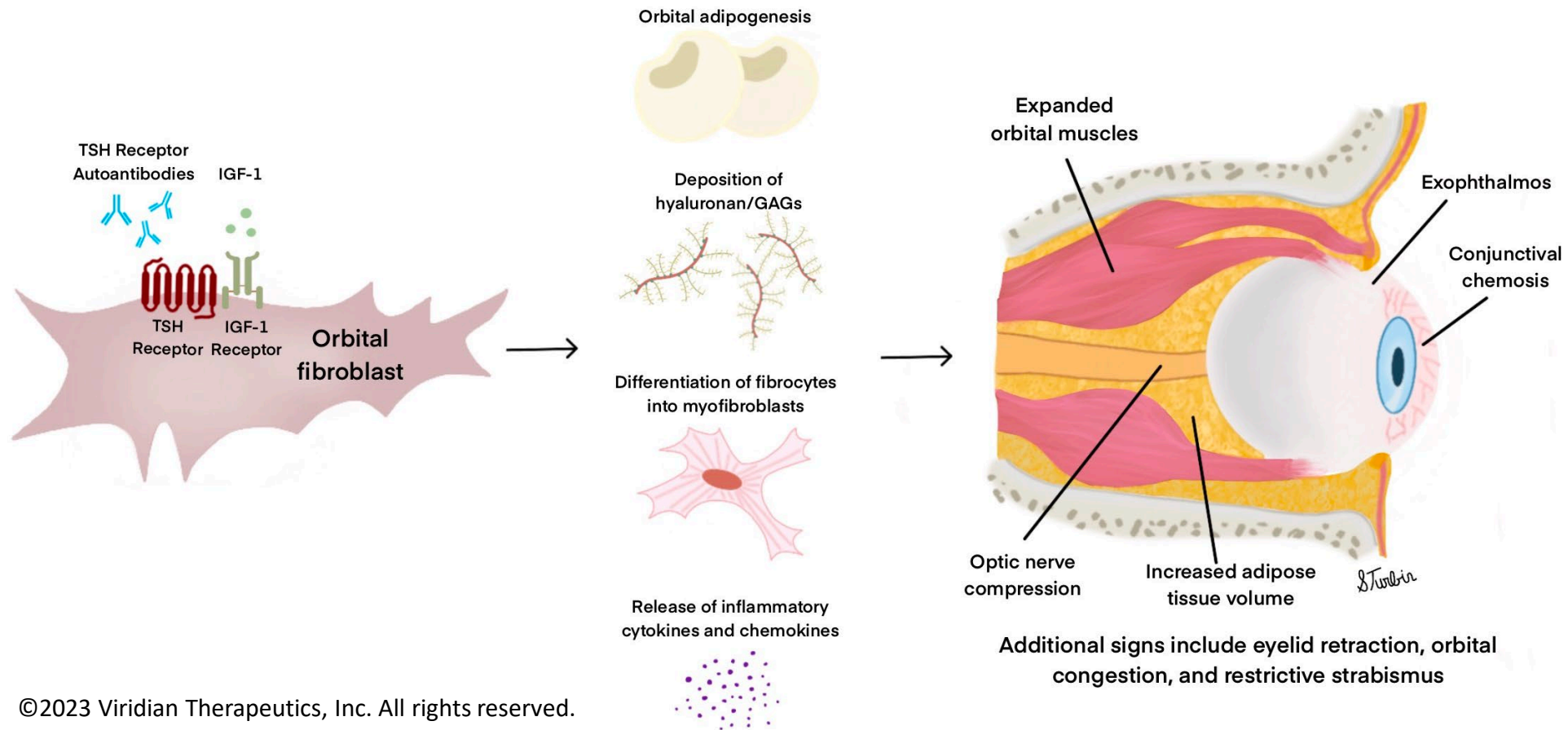
# Learning objectives

## Better understand:

- Thyroid eye disease (TED) pathophysiology
- **VRDN-001** preclinical data, **VRDN-001** distinct binding and antagonist properties
- **VRDN-001** phase 2 proof-of-concept (POC) study results

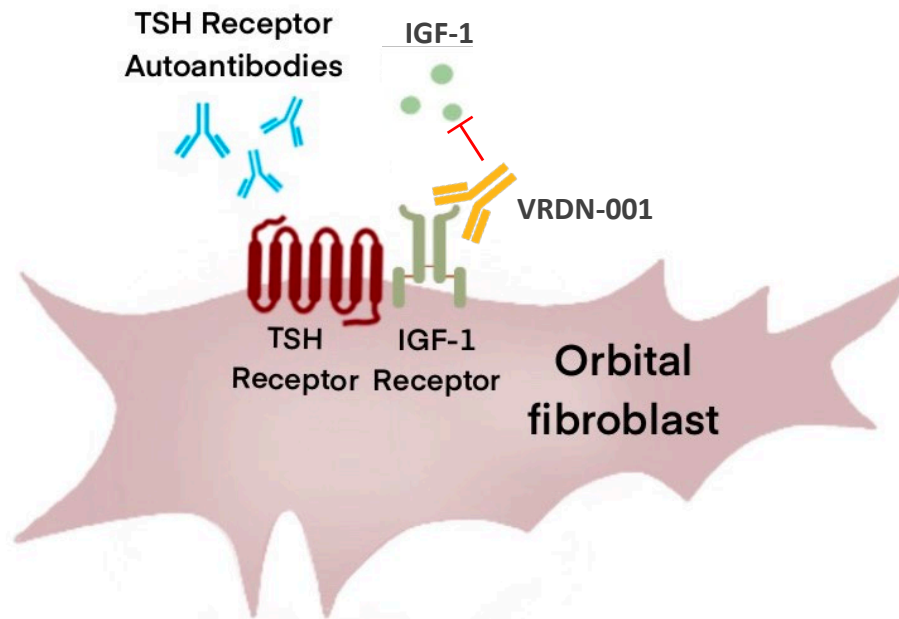
# Thyroid eye disease (TED) pathophysiology

# TED: Stimulation of TSHR/IGF-1R signaling complex results in inflammation and tissue expansion in the fixed bony orbit



**VRDN-001 preclinical data:  
distinct binding & antagonist  
properties**

# VRDN-001, full antagonist antibody to IGF-1R, for treatment of TED



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- **VRDN-001** is a monoclonal antagonist antibody against the IGF-1 receptor, and is currently in development for the treatment of TED
- In preclinical studies, **VRDN-001**:
  - Completely inhibits IGF-1 ligand binding to IGF-1R\*
  - Completely antagonizes IGF-1R proximal and distal signaling\*
- **VRDN-001** administration:
  - Currently being developed as intravenous formulation
  - Potential for subcutaneous formulation

\*Zhao Y et al. VRDN-001, A Strong Antagonist Antibody to the Insulin-Like Growth Factor Receptor-1 (IGF-1R) in Development for Thyroid Eye Disease (TED), Binds to a Distinct Epitope From Teprotumumab. Late Breaking Highlighted Poster 132. *Thyroid*. 2022;32(1).

**VRDN-001 phase 2 proof-of-  
concept study results in *active* TED**



# Proof-of-concept randomized, double-masked trial tested 3 different doses in active TED

Patients received 2 infusions 3 weeks apart

Patients with active TED:

- Clinical activity score (CAS) of  $\geq 4$
- Onset of signs/symptoms within prior 12 months

Placebo  
(n=6\*)

VRDN-001 3 mg/kg  
(n=9)

VRDN-001 10 mg/kg  
(n=6)

VRDN-001 20 mg/kg  
(n=6)

\*One patient in the placebo arm discontinued the study before Week 6 and thus is not included in the efficacy analysis but is included in the safety analysis.

# Baseline patient characteristics

	<b>VRDN-001 (3, 10, and 20 mg/kg)</b>	Placebo
n	21	5
Proptosis, mean (SEM)	23.7 (0.7)	22.8 (2)
CAS, mean (SEM)	5.4 (0.2)	5.0 (0.5)
Diplopia, n (%)	13 (62%)	3 (60%)
Gorman diplopia score, mean (SEM)	1.3 (0.3)	1.6 (0.7)
Months since onset of TED signs/symptoms, mean (SEM)	7.4 (0.8)	7.0 (2.0)
Age, mean years (SEM)	47 (3.3)	44.2 (4.3)
Female, n (%)	19 (90%)	3 (60%)

SEM = Standard error of the mean

# Summary of VRDN-001 outcome measures

Preliminary data after 2 infusions (6 weeks)

Week 6	Overall responder rate	Proptosis responder rate	Proptosis mean change by Hertel	CAS score of 0 or 1	CAS mean change	Diplopia complete resolution*
<b>All VRDN-001, n=21</b>	<b>67%</b>	<b>71%</b>	<b>-2.3 mm</b>	<b>62%</b>	<b>-4.1</b>	<b>54%</b>
3 mg/kg, n=9	56%	67%	-2.7 mm	67%	-4.2	20%
10 mg/kg, n=6	83%	83%	-2.4 mm	83%	-4.3	75%
20 mg/kg, n=6	67%	67%	-1.7 mm	33%	-3.7	75%

\*Includes only patients who had diplopia present at baseline. Diplopia was present at baseline in 13 out of 21 drug-treated patients (mean Gorman score of 2.2); 4 in 10 mg/kg cohort, 4 in 20 mg/kg cohort, and 5 in 3 mg/kg cohort.

Overall responder rate: % of patients with  $\geq 2$ -mm reduction in proptosis and  $\geq 2$ -point reduction in CAS

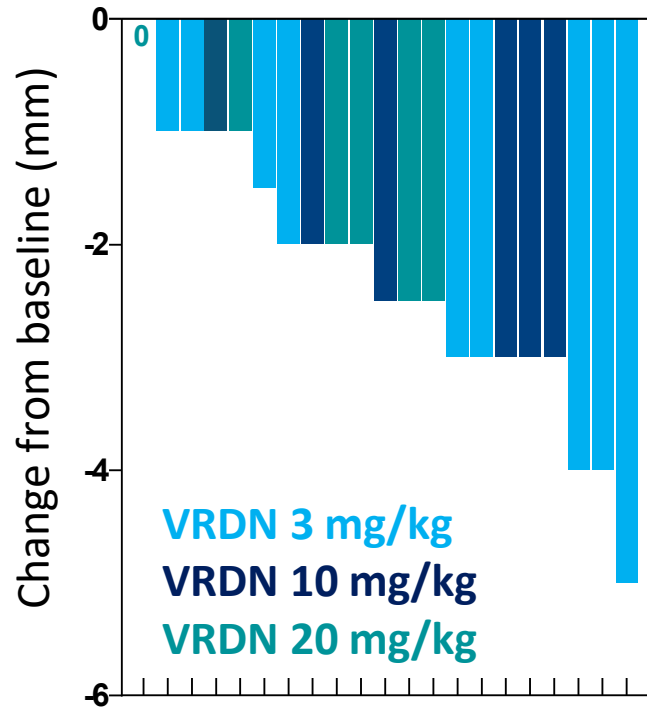
Proptosis responder rate: % of patients with  $\geq 2$ -mm reduction in proptosis measured by exophthalmometry

Clinical activity score (CAS): a composite 0-7 scale scoring signs and symptoms of TED

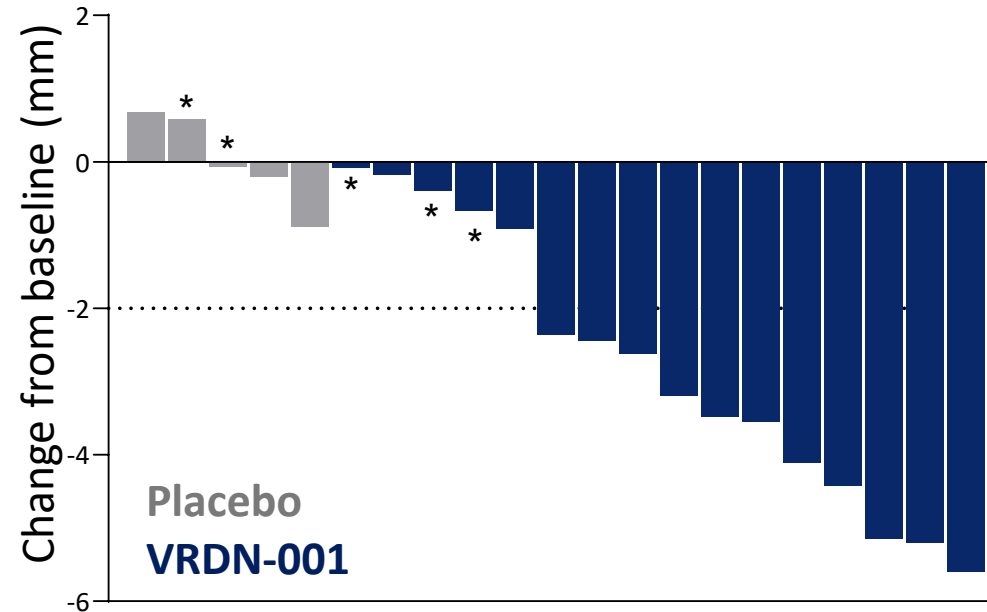
# Proptosis reductions by exophthalmometer and MRI/CT

Preliminary data after 2 infusions (6 weeks)

Individual Hertel proptosis change  
(all VRDN-001 patients)

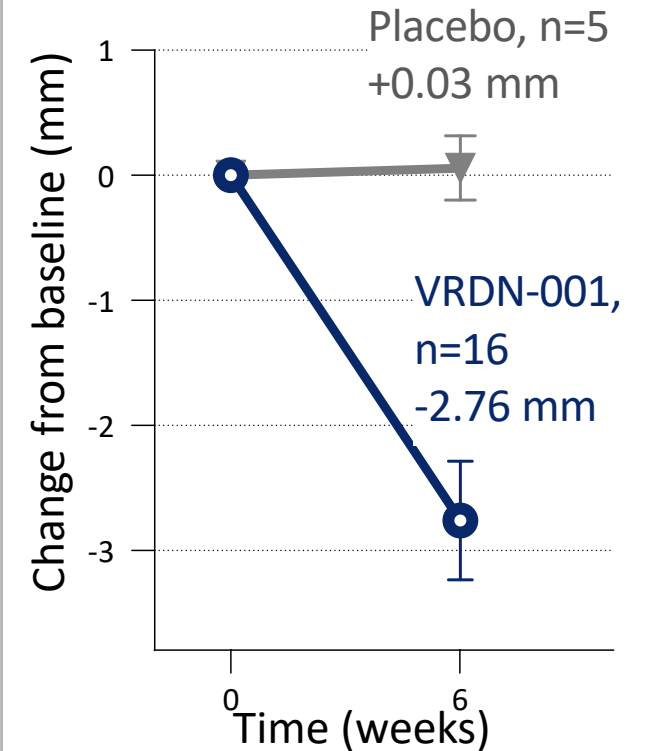


Individual MRI/CT proptosis change  
(all patients with scans\*\*)



\*\*2 placebo patients and 3 VRDN-001 patients were proptosis responders by Hertel exophthalmometer, but response was not confirmed by MRI/CT.

Mean MRI/CT proptosis change  
(all patients with scans\*\*)

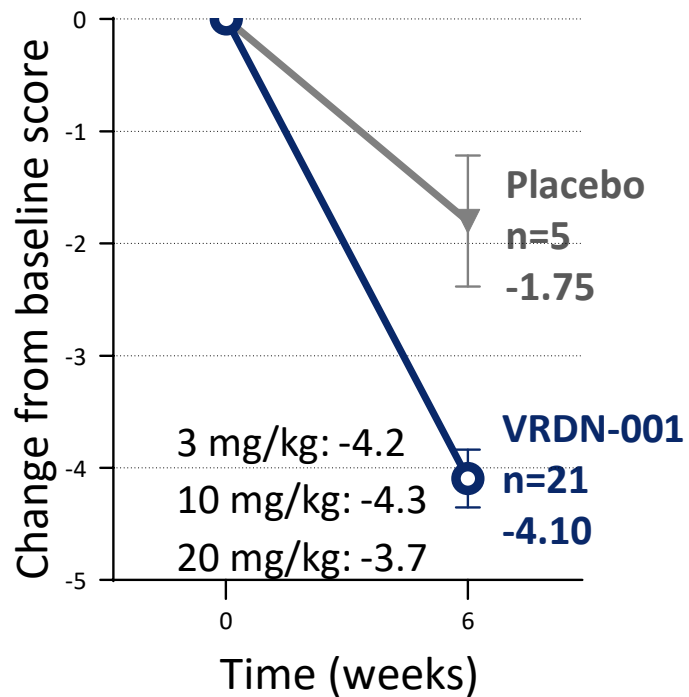


\*\*Masked, centrally reviewed MRI/CT data were available for 5 of 5 placebo patients and 16 of 21 VRDN-001 patients. All MRI/CT images were reviewed centrally by 2 independent, masked readers.

# Improvement in CAS

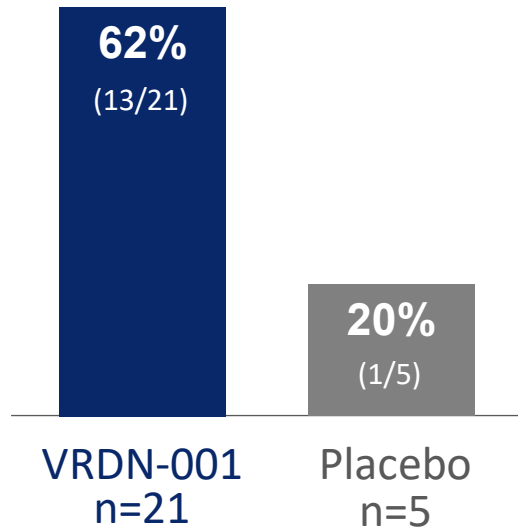
Preliminary data after 2 infusions (6 weeks)

Mean change in CAS  
(from baseline to Week 6)

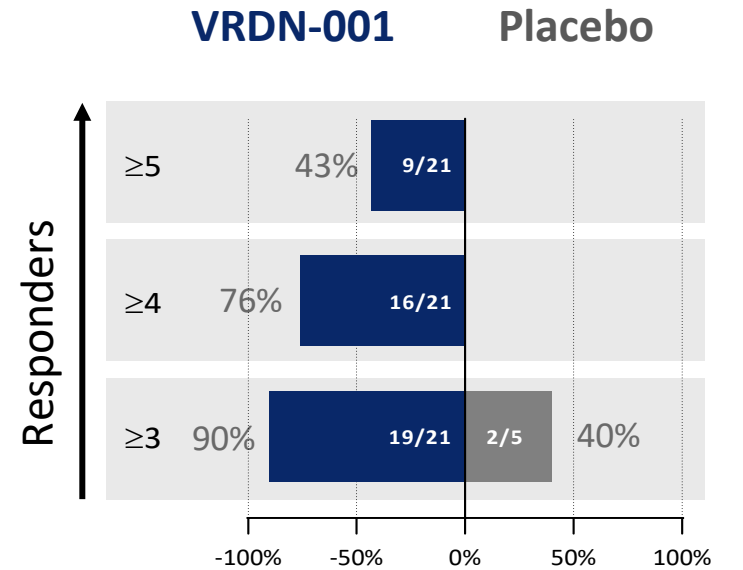


CAS of 0 or 1 at Week 6

3 mg/kg: 67%  
10 mg/kg: 83%  
20 mg/kg: 33%

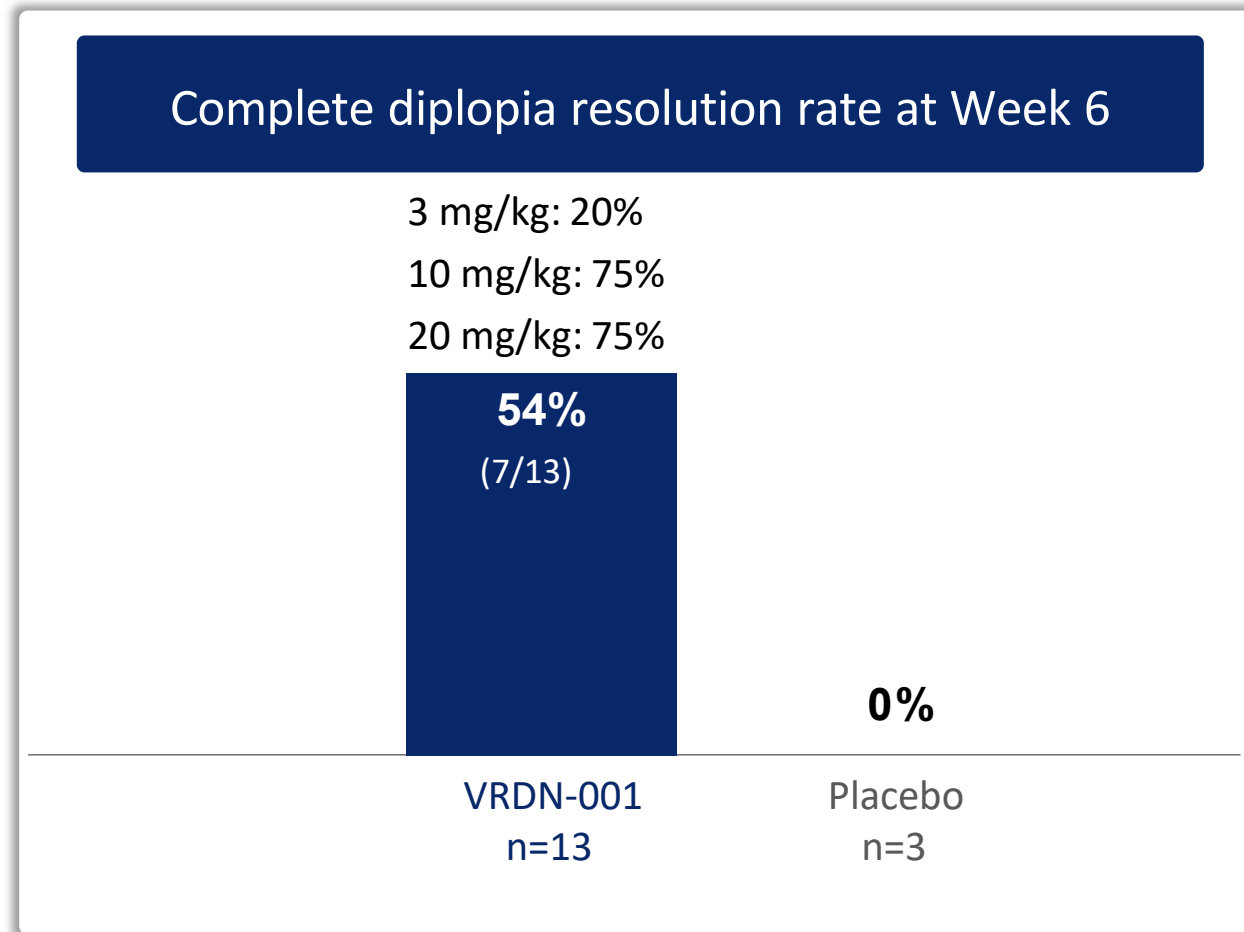


Reduction in CAS  
(from baseline to Week 6)



# Complete diplopia resolution by Gorman score

Preliminary data after 2 infusions (6 weeks)



Diplopia resolution rate defined as % of patients with diplopia at baseline whose diplopia completely resolved

Diplopia was present at baseline in 13 out of 21 drug-treated patients (mean Gorman score of 2.2) and 3 out of 5 placebo patients (mean Gorman score of 2.8).

# Safety profile

Preliminary data

No serious adverse events (SAEs), infusion reactions, or discontinuations

\*Deemed unrelated to study drug by the masked investigators.

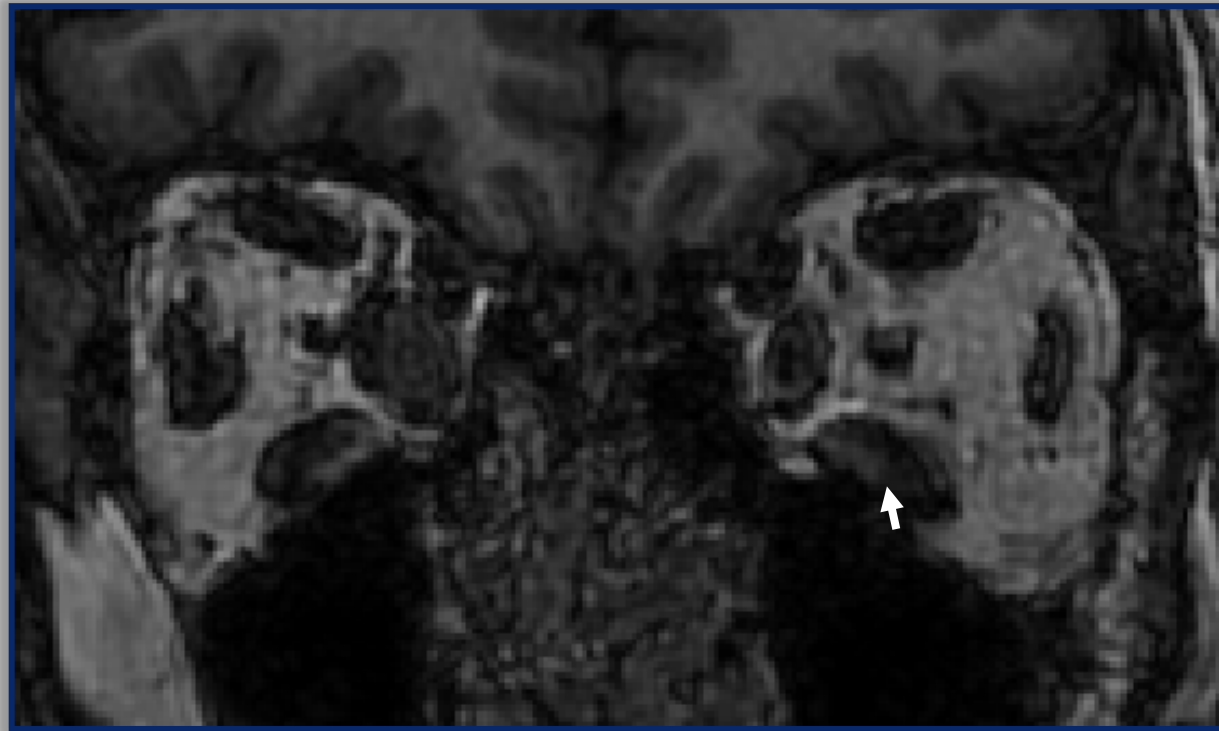
\*\*1 patient deemed related and 1 patient deemed unrelated to study drug by the masked investigators.

Data are as of data cutoff of December 19, 2022. Other AE that occurred in more than 1 patient and deemed related to study drug by masked investigators was acne (n=2). Instances were mild and did not require intervention. Muscle spasms were mild and did not require intervention; hearing impairment (n=2) resolved without intervention in both cases. Both patients with hyperglycemia were diabetic at baseline; in 1 case glucose variability was determined by masked PI to be unrelated to drug.

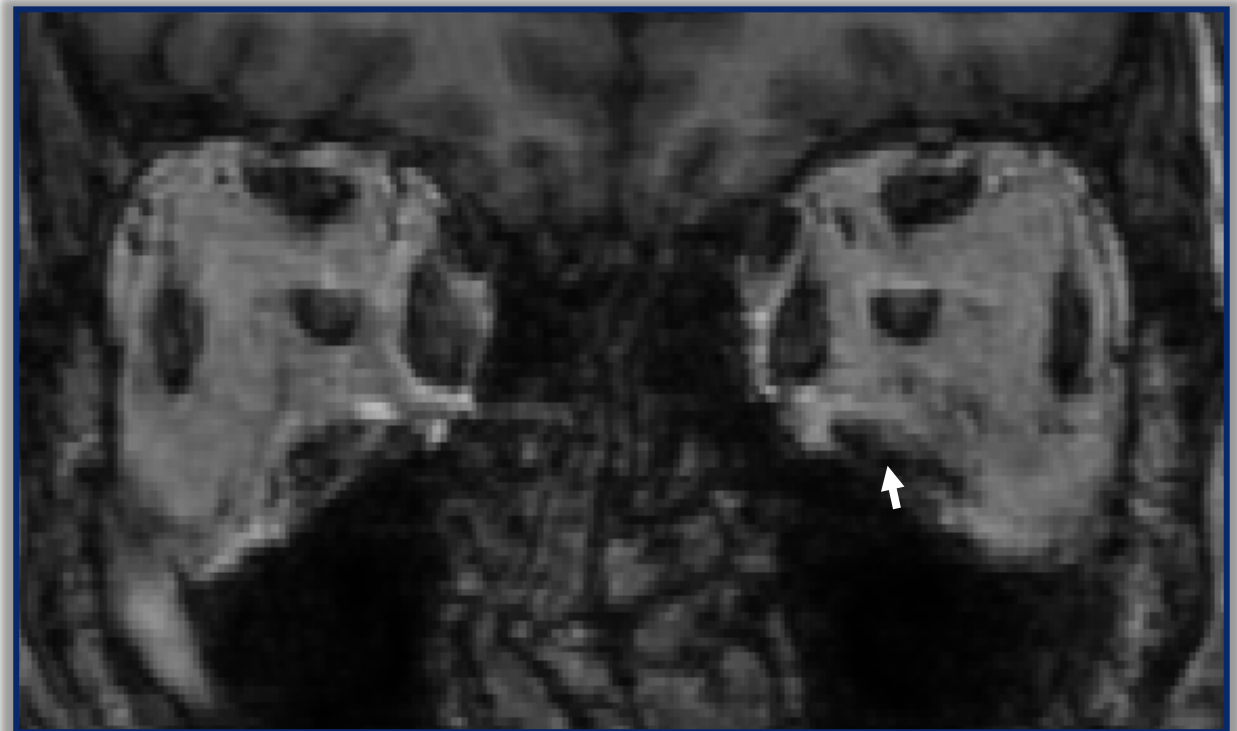
Adverse Reactions	VRDN-001 3 mg/kg (n=9), n	VRDN-001 10 mg/kg (n=6), n	VRDN-001 20 mg/kg (n=6), n	Placebo (n=6), n
Muscle spasms	2	2	2**	-
Nausea	2	-	-	-
Alopecia	-	-	-	1
Diarrhea	1	2**	1*	-
Fatigue	-	1	-	3
Hyperglycemia	1	-	1*	-
Hearing impairment	1	1	-	-
Dysgeusia	-	-	1	-
Headache	2	1	1	2**
Dry skin	1	-	1	-
Infusion reactions	-	-	-	-

# Patient #1

Baseline (Week 0)



After 2 **VRDN-001** infusions (Week 6)



White arrows highlight reduction in size of the inferior rectus muscle.



# Patient #2

Baseline at Week 0



2 days before first infusion of **VRDN-001**

Week 6



2 days following second infusion of **VRDN-001**

Patient photos taken by patient used with patient and investigator permission. Patient received 2 infusions in the study; in extended follow-up off treatment, TED symptoms have returned for this patient.

# Conclusions

- **VRDN-001** shows distinct binding and antagonist properties
- Preliminary phase 2 POC results show 2 IV infusions of **VRDN-001** were well tolerated and led to meaningful improvements in symptoms of active TED
  - Similar results were observed in **VRDN-001** POC study of chronic TED (ESOPRS presentation)
- The safety and efficacy of **VRDN-001** will be further assessed in the ongoing THRIVE (active TED; NCT05176639) and planned THRIVE-2 (chronic TED; NCT06021054) phase 3 clinical trials

# Thank you! Questions?

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